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SEX DIFFERENCES IN TRAJECTORIES OF DEPRESSION SYMPTOMS AND ASSOCIATIONS WITH 10-YEAR MORTALITY IN STROKE PATIENTS: THE SOUTH LONDON STROKE REGISTER

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Running Title: Sex differences in trajectories of depression after Stroke

Key Words: Depression; Stroke; Sex; Hospital Anxiety and Depression Scale (HADS); Group Based Trajectory Modelling (GBTM); Mortality

Abstract

Background:

Depression is a common neuropsychiatric consequence of stroke. We identified trajectories of depression symptoms in men and women and examined their associations with 10-year all-cause mortality.

Methods:

Data were obtained from the South London Stroke Register (1998-2016). Socio-demographic, stroke severity and clinical measures were collected during the acute phase. The Hospital Anxiety and Depression Scale (HADS) was used to screen for depression at 3 months after stroke then annually. We used Group Based Trajectory Models (GBTMs) to identify trajectories of depression, and Cox proportional hazards models to study the risk of mortality in these.

Results:

We studied 1275 men and 1038 women. Three trajectories of depression symptoms were identified in men: I-M (42.12%) low and stable symptoms, II-M (46.51%) moderate increasing, and III-M (11.37%) severe persistent. In women four trajectories were identified (I-F to IV-F); 29.09% with low symptoms, 49.81% moderate, 16.28% severe, and 4.82% with very severe symptoms. Ten-year mortality hazard ratios (HRs) in men were: 1.68 (95% CI:1.38-2.04) and 2.62 (1.97-3.48) for the trajectories II-M, and III-M respectively, compared to I-M. In women these were: 1.38 (1.09 – 1.75), 1.65 (1.23 – 2.20) and 2.81 (1.90 – 4.16), for trajectories II-F, III-F, and IV-F respectively compared to I-F.

Conclusions:

Depression trajectories varied independent of sex. Severe symptoms in women are double these in men. Moderate symptoms in men get worse overtime. Increased symptoms of depression are associated with higher mortality rates. Data on symptoms progression may help a better long-term management of stroke patients.

Introduction

Symptoms of depression are common after stroke and have long term consequences, including slow recovery, poor quality of life and higher mortality.[1] Systematic reviews have estimated the overall prevalence of depression post stroke at approximately 30%.[2, 3] Most attention has been given to the prevalence, predictors and outcomes. A systematic review of 47 studies, has shown slightly higher prevalence of depression in women compared to men and highlighted substantial variations in estimates for both sexes, with a prevalence varying from 4.7% to 66.7% in men, and between 5.9% to 78.3% in women.[4] Reasons for these variations include, assessments at different times after stroke, differences in settings, the use of different diagnostic tools, and different choices of thresholds that define depression. Some studies have used validated scales such as the hospital anxiety and depression scale (HADS) and the general health questionnaire (GHQ), and some have designed new questionnaires, whereas few studies have used a standardised clinical interview (DMS-III and DMS-IV) to diagnose depression.

Methods that assume individuals belong to a single population, overlook patients' heterogeneity and are unable to detect varying patterns of variables change over time. Group Based Trajectory Models (GBTMs) allow the identification of clusters of individuals that follow similar developmental trajectory on predictors and outcomes, and their long-term consequences.[5]

This study aims to test the hypothesis that men and women have the same trajectories of depression following stroke, using GBTMs. In addition, we aim to investigate associations between different trajectories and 10-year all-cause mortality.

Methods

Patients with first ever stroke were recruited between 1998 and 2016 from the South London Stroke Register (SLSR), a prospective population-based cohort study, and were followed up to July 2017. The World Health Organization (WHO) definition of stroke was used.[6] The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) [7] recommendations were used to report the flow of patients from registration, and the numbers who filled the HADS questionnaire to 5 years after stroke, reported previously[8]. Data collected during the acute phase included socio-demographic factors, comorbidities and stroke severity indicators including Glasgow Coma Scale (GCS), incontinence, and paresis. Patients were assessed at 3 months, one year after stroke, and then annually. Follow up at 3 months was by postal questionnaire or interview. At follow up patients were screened for depression using the Hospital Anxiety and Depression scale (HADS).[9] The scale has been validated in stroke patients and in the general population.[10]

Patients with impaired communication were not assessed by HADS. Disability was assessed using the Barthel Index (BI) categorised as severe disability (0-14); moderate (15-19) and independent. The scale was validated for use in stroke patients and has excellent reliability.[11]

Statistical analysis

HADS-D (depression domain) scores, over five years after stroke were used to derive varying trajectories of symptoms. Initially all participants who responds to HADS between 3 months and end of study follow up date (July 2017), in 3 occasions or more were included in the analysis. A specialised GBTMs algorithm was used to identify trajectories and to calculate the posterior probabilities for each. [12] A range of (1-6) trajectories was proposed, and 3 shapes were examined: First order (constant over time), second order (increase or decrease over time) and third order polynomial function (increase then decrease or vice versa). The selection of best fit model was based on three recommended goodness of fit criterion: (1) A minimum Bayesian Information Criterion (BIC), (2) High posterior probabilities of assigning patients to trajectories, and (3) A meaningful composite of each trajectory, judging the similarity and differences between trajectories, the size of each, and the usefulness in practice.[5, 13]

To test the robustness of the results, we applied the final models obtained to samples with different inclusion criteria as sensitivity analyses. The samples included: (a) Patients who had survived five years or more after stroke, and responded to HADS in at least three occasions, (602 men, and 460 women); (b) Patients with 3 or more measurements of HADS between 3 months to 5 years after stroke, regardless of survival (683 men, and 542 women), and (c) half of the data, splitting men and women by random numbers which comprised (610 vs. 665) for men and (522 vs. 516) for women.

Estimated means and proportions of socio-demographic characteristics and stroke severity indicators were reported by sex and by trajectory. No formal tests were used to compare estimates across trajectories, with exception of a few selections, due to the large number of comparisons and the likely inflation of Type I error.[14]

Cox regression models were used to compute hazard ratios (HRs) of mortality and 95% confidence intervals, for each trajectory. Unadjusted, and age and severity indicators adjusted, HRs were estimated. Trajectories with lowest depression symptoms (I-M and I-F) were used as references. The outcome was defined as death within 10-year of stroke. Time to outcome was defined as time from stroke onset to death, or to 21 July 2017 for participants who were still alive. Individuals were censored, if they reached 21 July 2017 alive or were lost to follow. The severity indicators and socio-demographic factors described in Table 2, were used as potential confounders. Stata 14.1[15] was used for all analyses, and the programme Mata was utilised to calculate adjusted survival probabilities by age quartiles. [16]

RESULTS

The main analysis comprised 1275 men and 1038 women. Three trajectories of symptoms of depression were identified in men (I-M, II-M, and III-M), and four in women (I-F, II-F, III-F, and IV-F). The predicted mean scores and shapes of growth of symptoms over time were given in Table1. Figure1, displays: the trajectories (solid lines), 95% confidence intervals (dashed lines) alongside the observed mean HAD-D scores (diamonds) for men and women. Trajectories, III-M, III-F, and IV-F, have average scores above the threshold (8 +) used to identify major depression[17], throughout the 5 years of observation. Moderate symptoms in men get worse over time whereas these, remain the same in women. Using the inclusion criteria (a) to (c) described in methods, provided consistent results with those obtained in the main analysis.

Table 2 show that between 76% to 94% of patients were physically independent pre- stroke, while between 18% to 51% were independent in the acute phase. Men with most severe depression symptoms (III-M) were slightly younger than others. Women were generally older than men, and group I-F (lowest level of symptoms) were on average younger than others, as opposed to men. Trajectories with more symptoms of depression have significantly higher proportions of Asians (Indians, Pakistani, Bangladeshi and Chinese), higher prevalence of incontinence, physical limitations and lack of orientation in the acute phase.

The risk of 10-year all-cause mortality increases as symptoms of depression increase for both sexes. Unadjusted, and adjusted HRs were significantly higher for trajectories II-M and III-M compared to I-M in men, and for II-F, III-F, and IV-F compared to I-F, in women. Adjustment for age and severity indicators altered the magnitude of the estimates slightly but didn't affect their significance. Age was the only predictor that remains significant after adjusting for all other confounders. Table 3

The adjusted survival estimates of depression trajectories and age quartiles (Q1: ≤ 60; Q2: > 60 -71.8; Q3: > 71.8-80.9; Q4: 81+ years) diplayed in Figure 2, show that as depression symptoms increase survival probabilities of patients in the same age quartile decrease. For example, the 10-year survival probabilities for patients in the first age quartile (Q1) were 0.9 for trajectory I-M, 0.75 for trajectory II-M, and 0.65 for trajectory III-M. The corresponding probabilities, in the second quartile (Q2) were, 0.65, 0.55, and 0.45 across the three trajectories respectively. Lower probabilities with similar patterns were observed for Q3 and Q4. Figure 2 (a)

For women, similar patterns were observed but some differences were noted. For Q1, for example, the survival probabilities across the 4 trajectories (I-F to IV-F) were approximately: 0.95, 0.9, 0.85 and 0.75, higher than those for men in Q1. For the second and third age

quartiles, these were close for the two sexes. Figure 2 (b) For the fourth quartile (Q4), the probabilities were below 0.25 for both sexes and approaches zero, for the trajectories with the worst symptoms of depression III-M, and IV-F.

DISCUSSION

Using a group-based approach to study the developmental course of depression in stroke patients uncovered sex differences and provided evidence to reject the null hypothesis that men and women have the same trajectories of depression. In addition, the segmentation of data offered estimates of increased mortality risk for trajectory groups with increased depression symptoms. Such details may help researchers and clinicians to revise and more clearly articulate predictions, develop and test taxonomic theories, and supplement a largely controversial evidence on the relationship between depression after stroke and mortality.[18]

Over 10% of men have long term severe symptoms (III-M) and 20% of women have severe or very severe symptoms (III-F and IV-F) that persist over time. The average HADS-D scores, among the trajectories of men and women with most severe symptoms, were greater "8+" that is widely recognised as an indicator of major depression. [19] The age adjusted survival estimates illuminated the age and depression interactions and highlighted the dramatic decrease in survival probabilities as depression symptoms increase within an age quartile that was shared by both sexes.

Awareness of differential depression symptoms may help elucidate a more complex reality of depression and offers better understanding of the natural history of depression and the relationship between depression and sex differences that is found to be inconsistent. [20]

The higher prevalence of depression among women may reflect the higher prevalence in the general population where depression was identified as the leading cause of disease burden in women worldwide.[21] Although the aetiology is yet to be established, researchers have nonetheless identified a combination of reasons that are likely to have a role in the increased risk in women. Studies on twins, have shown a stronger genetic tendency to depression in women compared to men.[22] Others proposed psychosocial, genetics, and epigenetics causes, or suggested that differences are at least partially driven by hormonal influences in the brain.[23] Among stroke patients all or some of these factors may have contributed to the increased risk among women. Of some relevance perhaps, is the believe that women draw larger components of their sense of self and self-worth from interpersonal relationships, and networks, and they are more sensitive to adversities of these. As women live longer, they are therefore, more exposed to loneliness, poor physical health, loss of social support, and the negative impact of these that predispose to depression.

Although physical limitations, and poor networks were known to be common among people with depression symptoms, and to be associated with increased risk of mortality, the mechanisms of how these operate and the pathways to mortality are not fully understood. A recent meta-analysis on 308,849 older adults, followed for an average of 7.5 years, reported a 50% increased survival among people with adequate social relationships compared to those with poor or insufficient social relationships.[24]

While the association between severe depression symptoms and mortality in stroke patients has been reported[4, 25], sex differences and differential trajectories of symptoms over time demonstrated in this study, to our knowledge, were not previously explored.

Understanding developmental trajectories has previously helped in better understanding of causal pathways, such as the developments of social behaviours into offending, childhood depression into mental illness, and in understanding heterogeneity of patients in response to treatments.[26]

Study strengths: the use of long term follow up data from an established stroke register, covering 88% of stroke incidents occurring in the study area[27]; a completion rate of HADS of over 75%; the use of GBTMs to unmask the heterogeneity in the developmental course of depression by sex.

Study limitations: a loss to follow up of around 20%. Patients who miss an assessment however, are often captured in subsequent assessments, and therefore provide information that can be used in models of repeated measures, such as those used in this study, where all available measures are used irrespective of intermittent missingness. Additionally, part of the missing data was due to the inability of some patients with cognitive or communication impairment to respond to the HADS. While this may introduce bias, estimates in the main baseline characteristics from patients with complete data showed no significant differences from those lost to follow up, suggesting missingness is likely to be missing at random (MAR) and not systematic.[5]

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Ethics: Patients or their relatives gave written informed consent to the SLSR field workers at the time of registration. The ethics committees of Guy's and St. Thomas' Hospital National Health Service Foundation Trust, King's College Hospital Foundation, National Hospital for Nervous Diseases, Queen's Square Hospital, St. George's Hospital, and Westminster Hospital approved the study.

Conflict of interest: None

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Figure 1.

Trajectories of depression five years after stroke in men and women

Legend: Observed means(diamonds); predicted trajectories(solid lines); 95% Confidence intervals(dashed lines).

Figure 2.

Adjusted survival functions for combinations of trajectories of depression and age quartiles in men and women

(a) Men

(b) Women

Legend: Q1-Q4: Age quartiles[Q1: ≤ 60; Q2: > 60 -71.8; Q3: > 71.8-80.9; Q4: 81+ years]

Table 1. Parameter estimates for the 4 models and posterior probabilities of assignment to trajectories

Full analysis	Class	Trajectory Shape	Predicted mean score	(SE)	Posterior probability	(SD)
Men	I	Intercept	2.03	0.22	0.85	0.15
		Slope	0.16	0.06		
	II	Intercept	6.04	0.27	0.80	0.15
		Slope	0.33	0.06		
	III	Intercept	12.44	0.33	0.83	0.17
Women	I	Intercept	2.51	0.20	0.78	0.17
	II	Intercept	6.16	0.24	0.75	0.14
	III	Intercept	10.27	0.40	0.74	0.17
	IV	Intercept	15.16	0.50	0.80	0.16

Table 2. Demography and stroke severity in the acute phase for men and women classified by trajectories of depression

Gender	Men				Women				
Trajectory (Group)	I-M	II-M	III-M	All	I-F	II-F	III-F	IV-F	All
Group size n	537	593	145	1275	302	517	169	50	1038
(%)	42.12	46.51	11.37		29.09	49.81	16.28	4.82	
Age, mean	64.63	65.80	63.86	65.09	66.09	70.61	67.89	71.03	68.87
SD	13.60	13.13	13.06	13.33	16.95	14.52	15.94	15.63	15.66
Ethnicity									
White	65.7	62.07	70.92	64.59	66.33	62.9	62.5	70.00	64.17
Black	27.52	27.59	15.6	26.19	26.19	31.75	28.57	12.00	28.64
Asian	4.26	9.31	13.48	7.68	6.12	4.17	8.33	16.00	6
Unknown	2.52	1.03	0	1.54	1.36	1.19	0.6	2.00	1.18
BI pre-stroke	%	%	%	%	%	%	%	%	%
Severe limitations (0-14)	0.37	1.69	5.52	1.57	2.98	4.64	3.55	8.00	4.14
Moderate limitations (15-19)	3.54	9.27	8.28	6.75	8.94	15.09	14.2	16.00	13.2
Independent (20)	93.85	85.33	83.45	88.71	85.76	77.56	78.11	76.00	79.96
Unknown	2.23	3.71	2.76	2.98	2.32	2.71	4.14	0	2.7
BI at the acute phase									
Severe limitations (0-14)	19.37	35.41	42.07	29.41	23.18	39.65	42.6	50.00	35.84
Moderate limitations (15-19)	14.53	16.36	15.17	15.45	16.56	20.31	17.16	20.00	18.69
Independent (20)	51.21	30.35	28.28	38.9	45.03	23.98	24.26	18.00	29.87
Unknown	14.9	17.88	14.48	16.24	15.23	16.05	15.98	12.00	15.61
Incontinence									
No	82.68	71.67	68.97	76.00	80.46	65.18	61.54	62.00	68.88
Yes	13.78	24.11	26.9	20.08	14.9	29.21	34.32	36.00	26.2
Unknown	3.54	4.22	4.14	3.92	4.63	5.61	4.14	2.00	4.91
Glasgow Coma Scale (verbal)									
Not fully oriented	10.8	13.15	19.31	12.86	9.93	15.47	21.3	14.00	14.74
Fully oriented	50.65	43.68	37.93	45.96	44.04	38.3	39.64	34.00	39.98
Unknown	38.55	43.17	42.76	41.18	46.03	46.23	39.05	52.00	45.28
Able to lift arm									
No	15.68	33.15	29.89	25.29	20.71	33.22	49.07	59.26	33.72
Yes	83.14	65.47	68.97	73.44	76.92	64.07	50	40.74	64.11
Unknown	1.18	1.38	1.15	1.27	2.37	2.71	0.93	0	2.17
Able to walk									
No	27.89	40.06	45.98	35.5	35.5	47.28	53.7	55.56	45.48
Yes	70.03	58.01	54.02	62.72	62.72	49.32	43.52	44.44	51.84
Unknown	2.08	1.93	0	1.78	1.78	3.4	2.78	0.00	2.68

Note. I-M to III-M stand for 3 trajectories of depression in men, and I-F to IV-F for 4 trajectories of depression in women.

Table 3. Ten-year mortality hazard ratios (HRs) and 95% C.I. by Trajectories of depression symptoms in 1275 men and 1038 women, stroke patients

Men (n = 1275)									
	n (%)	Unadjusted HR	95% CI.		P value	Adjusted HR	95% CI.		P value
Group I	537 (42.12%)	1.00				1.00			
Group II	593 (46.51%)	1.70	1.40	2.07	< 0.0001	1.68	1.38	2.04	< 0.0001
Group III	145 (11.37%)	2.00	1.50	2.65	< 0.0001	2.62	1.97	3.48	< 0.0001
Age						1.07	1.06	1.08	< 0.0001
Women (n = 1038)									
Group I	302 (29.09%)					1.00			
Group II	517 (49.81%)	1.67	1.33	2.12	< 0.0001	1.38	1.09	1.75	0.007
Group III	169 (16.28%)	1.73	1.29	2.31	< 0.0001	1.65	1.23	2.20	< 0.0001
Group IV	50 (4.82%)	2.98	2.02	4.41	< 0.0001	2.81	1.90	4.16	< 0.0001
Age						1.08	1.07	1.09	< 0.0001